62483/S10

AADA 62-483/S-010

JUL 14 1992

R.W. Johnson Pharmaceutical
Research Institute
Attention: Thomas P. Koestler, Ph.D.
Route 202, P.O. Box 300
Raritan, New Jersey 08869-0602

Dear Sir:

Reference is made to your supplemental antibiotic drug application dated June 25, 1992, submitted pursuant to Section 314.70(c)(Special Supplement-Changes Being Effected) of the Regulations, regarding your abbreviated antibiotic drug application for Grifulvin V® (Griseofulvin Oral Suspension), 125 mg/5 mL.

The supplemental application provides for revised container labels and "booklet" insert labeling.

We have completed the review of this supplemental application and it is approved. Our letter of January 26, 1984, detailed the conditions relating to the approval of this abbreviated application.

However, at the time of next printing or within 180 days, whichever comes first, revise your labeling as follows:

A. General Comment

We note your comments that you have revised the established name of the product in accordance with the current USP monograph. The current USP monograph lists the established name for this product as Griseofulvin Oral Suspension not Griseofulvin Microsize Oral Suspension. Please revise your labels and labeling to reflect the correct established name as follows:

Griseofulvin Oral Suspension
(microsize)

Furthermore, it is not necessary to repeat "Suspension" in the title since it already appears in the established name.

B. Container Label

Revise the dispensing recommendation to read:

Dispense in a tight, light-resistant container as defined in the official compendium.

C. Booklet

1. Front Panel

Add the dispensing recommendations as stated above.

2. DOSAGE AND ADMINISTRATION, Adults, paragraph 2

"1 gram" ("1" rather than "1.0")

Prepare and submit revised labels and labeling as a supplement to this application.

The material submitted is being retained in our files.

Sincerely yours,

/S/

Roger L. Williams, M.D. 7/14/92
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc;
HFD-638
HFD-600
HFC-130/JAllen
KShah/JPhillips JPhillips 7/14/92
hab 7/10/92
62483S.010
approval HFD-82

THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE
ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602

N .J. ______ REG. NO. [illegible]

NDA SUPPL FOR Label Revision

JUN 25 1992

Office of Generic Drugs
Center for Drug Evaluation & Research
Food and Drug Administration
Attn: DOCUMENT CONTROL ROOM #150
MPN II, HFD #600
5600 Fishers Lane
Rockville, Maryland 20857-1706

FPL

SPECIAL SUPPLEMENT - Changes Being Effected 21CFR 314.70(c)

AADA 62-483
GRIFULVIN V® Suspension

Dear Sir/Madam:

Reference is made to our approved Abbreviated Antibiotic Drug Application 62-483 for GRIFULVIN V® (griseofulvin microsize oral suspension) Suspension. Reference is also made to your letter dated April 2, 1992 (copy attached) which requested specific revisions to our container label and outsert labeling included in our February 26, 1992 Annual Report. At this time we submit herewith a "Special Supplement-Changes Being Effected" application pursuant to 21CFR 314.70(c) which contains product labeling for GRIFULVIN V Suspension which has been revised as requested.

To facilitate the review of the labeling contained herein, we wish to note that a one-piece container label/package outsert is being implemented for GRIFULVIN V Suspension. This new configuration replaces the current individual components and consists of a pressure-sensitive container label (which is identical to the current label) and an overlying package outsert that will be removed from the bottle at the time of dispensing. The one-piece construction of the label will facilitate the packaging process of GRIFULVIN V Suspension by easing its placement on the rounded-type bottles for this product.

The format of the package outsert portion of the one-piece label will be a "booklet" style rather than the standard pull-out style of the current outsert. The difference between the standard pull-out outsert and booklet outsert is in the outer panel. The standard outer panel will contain only the product name and the Ortho company signature. In contrast, the booklet outer panel will be identical to the underlying container label, except that the "see accompanying product literature" statement and the dispensing recommendations will be replaced by a "PULL DOWN TAB TO OPEN INFORMATION BOOKLET" statement. No other modifications to the text of the outsert will be necessary to accommodate the new booklet format.

ORIGINAL

RECEIVED
JUN 30 1992
GENERIC DRUGS

cim 7-1-92

The standard outsert that was the subject of your April 2, 1992 letter, along with the remaining GRIFULVIN V Tablet components will be revised in accordance with the Suspension labeling for consistency. Therefore, we plan to file a similar supplement to AADA 62-279 in the very near future.

As requested in your letter of April 2, 1992, we have deleted from our labeling the statement and deleted the statement of INDICATIONS found after the TITLE.

The following response addresses each point of your April 2, 1992 letter:

...revise your container labels as follows:

1. **Revise the established name to read**:

Griseofulvin Oral Suspension, USP
(microsize)

The established name on the container label and outer panel of the booklet outsert has been revised as requested. However, for consistency with the current USP monograph for this product, the established name has been changed to: griseofulvin microsize oral suspension.

Many of our products are designated in the current USP/NF. It is our understanding that if a product monograph appears in the USP/NF, and if the product is labeled with its compendial name it must comply with compendial standards unless specified otherwise. This is true regardless of whether or not the compendial title is accompanied by "U.S.P.". Accordingly, in general, it has been our company policy not to include the USP designation following such product's compendial name. This in fact has been our ongoing practice for the GRIFULVIN V products which we desire to continue.

In an effort to conserve limited space, and in accordance with 21CFR 201.10(g), we have deleted repetitions of the established name in the running text of the outsert since it accompanies the proprietary name on the outer panel. This revision affects the **Clinical Pharmacology, Indications and Usage** and the **How Supplied** sections of the booklet outsert.

2. **Include the strength (125 mg/5 mL) immediately after the established name in a prominent manner.**

The container label has been revised as requested. However, to conserve limited space and for consistency with our GRIFULVIN V Tablet container labels, we positioned the strength *under* the established name rather than immediately afterwards.

3. **Revise the expression of net quantity to read: 4 fl oz (120 mL)**

The container label has been revised as requested. For consistency, this change has also been made to the **How Supplied** section of the booklet outsert.

4. **Include dispensing recommendations, as seen in your insert labeling.**

Upon review of this request, we discovered inconsistencies between the dispensing recommendations in the outsert and that of the current USP monographs for griseofulvin microsize tablets and griseofulvin microsize oral suspension. Accordingly, the **How Supplied** section of the booklet outsert has been corrected to agree with the USP as follows:

FROM:

TO: Keep GRIFULVIN V Tablets in a tight container... compendium.
and
Keep GRIFULVIN V Suspension in a tight container... compendium.
Store in a light resistant container.

Therefore, the *correct* dispensing recommendation has been added to the container label for GRIFULVIN V Suspension as requested.

5. **Revise your USUAL DOSAGE statement to read:**

USUAL ADULT DOSAGE: Four teaspoonfuls (500 mg) daily.
USUAL CHILDREN'S DOSAGE: One (125 mg) to four (500 mg) teaspoonfuls daily...

The container label has been revised as requested.

The following minor changes were also made to the container label and/or booklet outsert for GRIFULVIN V Suspension:

a. Periods were deleted from the "mcg", "mg" and "gm" abbreviations used in the **Clinical Pharmacology, Dosage and Administration** and **How Supplied** sections of the booklet outsert. In addition, the abbreviation "cc" used in the **How Supplied** section was changed to "mL" for consistency. Also, the abbreviation "ml" has been changed to "mL" in the **ingredients** statement on the outer panel of the booklet outsert and the container label.

b. The trademark designation on the outer panel of the booklet outsert and the container label was changed from ™ to ®.

Appended herewith are, in final printed form, 12 mounted copies of the one-piece container label/booklet outsert for GRIFULVIN V Suspension. For your ease of review, the changes have been highlighted on separate pages which are attached to the mounted copies. For your convenience, a copy of the outsert and container label which was the subject of your April 2, 1992 letter has also been appended.

This revised labeling will be placed into effect immediately following submission of this supplement.

Should you have any questions, please contact me directly at (908) 704-4038.

Sincerely yours,

The R. W. Johnson
Pharmaceutical Research Institute

Thomas P. Koestler, Ph.D.
Senior Director
Regulatory Affairs

TPK/mlc
attachments

grifulvin\aada

NDC 0062-0206-04

Grifulvin V®

(griseofulvin microsize oral suspension)

Suspension 125 mg/5 mL

Each 5 mL (one teaspoonful) contains 125 mg griseofulvin microsize in a palatable suspension, colored orange. Also contains alcohol 0.2%.

Caution: Federal law prohibits dispensing without prescription.

Store at room temperature.

SHAKE BEFORE USING

Pharmacist: This product is protected by a tamper-resistant seal around the neck opening. If the seal has been broken or is removed, do not use the product. Return the product to place of purchase.

ORTHO

DERMATOLOGICAL DIVISION
ORTHO PHARMACEUTICAL CORPORATION
Raritan, New Jersey 08869
a Johnson & Johnson company

4 fl oz (120 mL)

USUAL ADULT DOSAGE: Four teaspoonfuls (500 mg) daily.
USUAL CHILDREN'S DOSAGE: One (125 mg) to four (500 mg) teaspoonfuls daily depending on age and weight.

PULL DOWN TAB TO OPEN INFORMATION BOOKLET.

NDDK

 U.S. Patents 2,900,304; 3,330,727 Made in U.S.A. 605-10-569-1

6505-01-137-8448

Description
Griseofulvin is an antibiotic derived from a species of *Penicillium*. Each GRIFULVIN V Tablet contains either 250 mg or 500 mg of griseofulvin microsize, and also contains calcium stearate, colloidal silicon dioxide, starch, and wheat gluten. Additionally, the 250 mg tablet also contains dibasic calcium phosphate. Each 5 mL of GRIFULVIN V Suspension contains 125 mg of griseofulvin microsize and also contains alcohol 0.2%, docusate sodium, FD&C Red No. 40, FD&C Yellow No. 6, flavors, magnesium aluminum silicate, menthol, methylparaben, propylene glycol, propylparaben, saccharin sodium, simethicone emulsion, sodium alginate, sucrose, and purified water.

Clinical Pharmacology
GRIFULVIN V acts systemically to inhibit the growth of *Trichophyton*, *Microsporum*, and *Epidermophyton* genera of fungi. Fungistatic amounts are deposited in the keratin, which is gradually exfoliated and replaced by noninfected tissue.

Griseofulvin absorption from the gastrointestinal tract varies considerably among individuals, mainly because of insolubility of the drug in aqueous media of the upper G.I. tract. The peak serum level found in fasting adults given 0.5 gm occurs at about four hours and ranges between 0.5 and 2.0 mcg/mL.

It should be noted that some individuals are consistently "poor absorbers" and tend to attain lower blood levels at all times. This may explain unsatisfactory therapeutic results in some patients. Better blood levels can probably be attained in most patients if the tablets are administered after a meal with a high fat content.

Indications and Usage
Major indications for GRIFULVIN V are:
- Tinea capitis (ringworm of the scalp)
- Tinea corporis (ringworm of the body)
- Tinea pedis (athlete's foot)
- Tinea unguium (onychomycosis; ringworm of the nails)

Tinea cruris (ringworm of the thigh)
Tinea barbae (barber's itch)

GRIFULVIN V inhibits the growth of those genera of fungi that commonly cause ringworm infections of the hair, skin, and nails, such as:

Trichophyton rubrum
Trichophyton tonsurans
Trichophyton mentagrophytes
Trichophyton interdigitalis
Trichophyton verrucosum
Trichophyton sulphureum
Trichophyton schoenleini
Microsporum audouini
Microsporum canis
Microsporum gypseum
Epidermophyton floccosum
Trichophyton megnini
Trichophyton gallinae
Trichophyton crateriform

Note: Prior to therapy, the type of fungi responsible for the infection should be identified. The use of the drug is not justified in minor or trivial infections which will respond to topical antifungal agents alone.

It is *not* effective in:

Bacterial infections
Candidiasis (Moniliasis)
Histoplasmosis
Actinomycosis
Sporotrichosis
Chromoblastomycosis
Coccidioidomycosis
North American Blastomycosis
Cryptococcosis (Torulosis)
Tinea versicolor
Nocardiosis

Contraindications

This drug is contraindicated in patients with porphyria, hepatocellular failure, and in individuals with a history of hypersensitivity to griseofulvin.

Two cases of conjoined twins have been reported in patients taking griseofulvin during the first trimester of pregnancy. Griseofulvin should not be prescribed to pregnant patients.

Warnings

Prophylactic Usage: Safety and efficacy of prophylactic use of this drug has not been established.

Chronic feeding of griseofulvin, at levels ranging from 0.5-2.5% of the diet, resulted in the development of liver tumors in several strains of mice, particularly in males. Smaller particle sizes result in an enhanced effect. Lower oral dosage levels have not been tested. Subcutaneous administration of relatively small doses of griseofulvin once a week during the first three weeks of life has also been reported to induce hepatomata in mice. Although studies in other animal species have not yielded evidence of tumorigenicity, these studies were not of adequate design to form a basis for conclusions in this regard.

In subacute toxicity studies, orally administered griseofulvin produced hepatocellular necrosis in mice, but this has not been seen in other species. Disturbances in porphyrin metabolism have been reported in griseofulvin-treated laboratory animals. Griseofulvin has been reported to have a colchicine-like effect on mitosis and cocarcinogenicity with methylcholanthrene in cutaneous tumor induction in laboratory animals.

Reports of animal studies in the Soviet literature state that a griseofulvin preparation was found to be embryotoxic and teratogenic on oral administration to pregnant Wistar rats. Rat reproduction studies done thus far in the United States and Great Britain have been inconclusive in this regard, and additional animal reproduction studies are underway. Pups with abnormalities have been reported in the litters of a few bitches treated with griseofulvin.

Suppression of spermatogenesis has been reported to occur in rats but investigation in man failed to confirm this.

Precautions

Patients on prolonged therapy with any potent medica-

Dosage and Administration

Accurate diagnosis of the infecting organism is essential. Identification should be made either by direct microscopic examination of a mounting of infected tissue in a solution of potassium hydroxide or by culture on an appropriate medium.

Medication must be continued until the infecting organism is completely eradicated as indicated by appropriate clinical or laboratory examination. Representative treatment periods are tinea capitis, 4 to 6 weeks; tinea corporis, 2 to 4 weeks; tinea pedis, 4 to 8 weeks; tinea unguium – depending on rate of growth – fingernails, at least 4 months; toenails, at least 6 months.

General measures in regard to hygiene should be observed to control sources of infection or reinfection. Concomitant use of appropriate topical agents is usually required, particularly in treatment of tinea pedis since in some forms of athlete's foot, yeasts and bacteria may be involved. Griseofulvin will not eradicate the bacterial or monilial infection.

Adults: A daily dose of 500 mg will give a satisfactory response in most patients with tinea corporis, tinea cruris, and tinea capitis.

For those fungus infections more difficult to eradicate such as tinea pedis and tinea unguium, a daily dose of 1.0 gram is recommended.

Children: Approximately 5 mg per pound of body weight per day is an effective dose for most children. On this basis the following dosage schedule for children is suggested:

Children weighing 30 to 50 pounds – 125 mg to 250 mg daily.

Children weighing over 50 pounds – 250 mg to 500 mg daily.

How Supplied

GRIFULVIN V 250 mg Tablets in bottles of 100 (NDC 0062-0211-60) (white, scored, imprinted "ORTHO 211").
GRIFULVIN V 500 mg Tablets in bottles of 100 (NDC 0062-0214-60) and 500 (NDC 0062-0214-70) (white,

6505-01-137-8448

tion should be under close observation. Periodic monitoring of organ system function, including renal, hepatic and hemopoietic, should be done.

Since griseofulvin is derived from species of penicillin, the possibility of cross sensitivity with penicillin exists; however, known penicillin-sensitive patients have been treated without difficulty.

Since a photosensitivity reaction is occasionally associated with griseofulvin therapy, patients should be warned to avoid exposure to intense natural or artificial sunlight. Should a photosensitivity reaction occur, lupus erythematosus may be aggravated.

Drug Interactions: Patients on warfarin-type anticoagulant therapy may require dosage adjustment of the anticoagulant during and after griseofulvin therapy. Concomitant use of barbiturates usually depresses griseofulvin activity and may necessitate raising the dosage.

The concomitant administration of griseofulvin has been reported to reduce the efficacy of oral contraceptives and to increase the incidence of breakthrough bleeding.

Adverse Reactions

When adverse reactions occur, they are most commonly of the hypersensitivity type such as skin rashes, urticaria and rarely, angioneurotic edema, and may necessitate withdrawal of therapy and appropriate countermeasures. Paresthesias of the hands and feet have been reported rarely after extended therapy. Other side effects reported occasionally are oral thrush, nausea, vomiting, epigastric distress, diarrhea, headache, fatigue, dizziness, insomnia, mental confusion and impairment of performance of routine activities.

Proteinuria and leukopenia have been reported rarely. Administration of the drug should be discontinued if granulocytopenia occurs.

When rare, serious reactions occur with griseofulvin, they are usually associated with high dosages, long periods of therapy, or both.

6505-01-137-8448

scored, imprinted "ORTHO 214").

Keep GRIFULVIN V Tablets in a tight container as defined in the official compendium.

GRIFULVIN V Suspension 125 mg per 5 mL in bottles of 4 fl oz (120 mL) (NDC 0062-0206-04).

Keep GRIFULVIN V Suspension in a tight container as defined in the official compendium. Store in a light-resistant container.

STORE AT ROOM TEMPERATURE

DERMATOLOGICAL DIVISION
ORTHO PHARMACEUTICAL CORPORATION
Raritan, New Jersey 08869
a Johnson & Johnson company

ORTHO

605-10-569-1

Issued May 1992

Printed in U.S.A.

U.S. Patent Nos. 2,900,304; 3,330,727

NDC 0062-0206-04

Grifulvin V®

(griseofulvin microsize oral suspension)

Suspension 125 mg/5 mL

Each 5 mL (one teaspoonful) contains 125 mg griseofulvin microsize in a palatable suspension, colored orange. Also contains alcohol 0.2%.

Caution: Federal law prohibits dispensing without prescription.

Store at room temperature.

SHAKE BEFORE USING

Pharmacist: This product is protected by a tamper-resistant seal around the neck opening. If the seal has been broken or is removed, do not use the product. Return the product to place of purchase.

DERMATOLOGICAL DIVISION
ORTHO PHARMACEUTICAL CORPORATION
Raritan, New Jersey 08869
a Johnson & Johnson company

ORTHO

4 fl oz (120 mL)

USUAL ADULT DOSAGE: Four teaspoonfuls (500 mg) daily.
USUAL CHILDREN'S DOSAGE: One (125 mg) to four (500 mg) teaspoonfuls daily depending on age and weight.
For information for use, see accompanying product literature.
Keep GRIFULVIN V Suspension in a tight container as defined in the official compendium. Store in a light-resistant container.

 Made in U.S.A. 605-10-569-1

6505-01-137-8448

FPL:
Package Insert "Booklet"
Container Labels
Satisfactory.
2-2-93

THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE
ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602

FEB 5 1993

Office of Generic Drugs
Food and Drug Administration
Center for Drug Evaluation & Research
Attn: DOCUMENT CONTROL ROOM #150
MPN II, HFD #600
5600 Fishers Lane
Rockville, Maryland 20857-1706

NDA NO. _____ REF. NO. SL 011
NDA SUPPL FOR _____

Amendment:
Final Printed Labeling

AADA 62-483/S-010
GRIFULVIN V® Suspension

FPL

Dear Sir/Madam:

Reference is made to our approved Abbreviated Antibiotic Application 62-483 for GRIFULVIN V Suspension and specifically to the Office of Generic Drugs (OGD) July 14, 1992 letter approving our Final Printed Labeling submitted on June 25, 1992 (letters appended). The OGD's July 14 letter requested additional revisions to the combined container label/booklet outsert at the time of next printing or within 180 days, whichever comes first.
As requested, we submit herewith 12 copies of Final Printed Labeling which contain the following revisions:

Established Name:
The established name has been revised as follows:

(griseofulvin oral suspension)
microsize

Please note that "microsize" appears outside of the brackets rather than inside as requested in your July 14, 1992 letter. This revised format was proposed to Mr. Kent Johnson, Associate Director, Labeling and Professional Support, Office of Generic Drugs during a telephone discussion between he and I regarding GRIFULVIN V Tablets on August 24, 1992. This format was later confirmed in our correspondence filed to AADA 62-279 for GRIFULVIN V Tablets (S-015) on September 14, 1992, and deemed acceptable by the Agency in an "approvable" letter dated October 23, 1992 (letters appended).

In addition, the established names for GRIFULVIN V Suspension and Tablets were inadvertently deleted from the "Description" section of the booklet outsert; this omission has been corrected accordingly.

RECEIVED
FEB 0 9 1993
GENERIC DRUGS

ORIGINAL

General Comment:
We acknowledge your comment that it is unnecessary to repeat "Suspension" in the product title since it already appears in the established name. However, to our knowledge, the current regulations do not preclude the repetition of this information and accordingly, we decline to remove it from the container label/booklet outsert.

Dispensing Recommendations:
The dispensing recommendations on the container label and booklet front panel have been revised as requested in your July 14, 1992 letter. However, in accordance with the Agency's preference delineated in the August 13, 1992 "approvable" letter for GRIFULVIN V Tablets (letter appended), the text reads as follows:

"Dispense in a tight, light-resistant container as defined in the USP"
(rather than "Dispense...as defined in the *official compendium*")

Dosage and Administration:
As requested, "paragraph 2, Adults" has been revised to read "1" gram rather than "1.0" gram.

Please be advised that the aforementioned changes were implemented on January 6, 1993.

Should you have any questions, please contact me directly at (908) 704-4038.

Sincerely yours,

The R. W. Johnson
Pharmaceutical Research Institute

Thomas P. Koestler, Ph.D.
Senior Director
Regulatory Affairs

TPK/mlc
attachment

grifulvin\aada

NDC 0062-0206-04

Grifulvin V®

(griseofulvin oral suspension)
microsize

Suspension 125 mg/5 mL

[redacted]

USUAL ADULT DOSAGE: Four teaspoonfuls (500 mg) daily.
USUAL CHILDREN'S DOSAGE: One (125 mg) to four (500 mg) teaspoonfuls daily depending on age and weight.
Dispense in a tight, light-resistant container as defined in the USP.
PULL DOWN TAB TO OPEN INFORMATION BOOKLET.
NDC/DK
 U.S. Patents 2,800,304; 3,330,727 Made in U.S.A. 606-10-569-2

6505-01-137-8448

Description

Griseofulvin is an antibiotic derived from a species of *Penicillium*. Each GRIFULVIN V (griseofulvin tablets) Tablet contains either 250 mg or 500 mg of griseofulvin microsize, and also contains calcium stearate, colloidal silicon dioxide, starch, and wheat gluten. Additionally, the 250 mg tablet also contains di-basic calcium phosphate. Each 5 mL of GRIFULVIN V (griseofulvin oral suspension) Suspension contains 125 mg of griseofulvin microsize and also contains alcohol 0.2%, docusate sodium, FD&C Red No. 40, FD&C Yellow No. 6, flavors, magnesium aluminum silicate, menthol, methylparaben, propylene glycol, propylparaben, saccharin sodium, simethicone emulsion, sodium alginate, sucrose, and purified water.

Clinical Pharmacology

GRIFULVIN V acts systemically to inhibit the growth of *Trichophyton, Microsporum,* and *Epidermophyton* genera of fungi. Fungistatic amounts are deposited in the keratin, which is gradually exfoliated and replaced by noninfected tissue.

Griseofulvin absorption from the gastrointestinal tract varies considerably among individuals, mainly because of insolubility of the drug in aqueous media of the upper G.I. tract. The peak serum level found in fasting adults given 0.5 gm occurs at about four hours and ranges between 0.5 and 2.0 mcg/mL.

It should be noted that some individuals are consistently "poor absorbers" and tend to attain lower blood levels at all times. This may explain unsatisfactory therapeutic results in some patients. Better blood levels can probably be attained in most patients if the tablets are administered after a meal with a high fat content.

Indications and Usage

Major indications for GRIFULVIN V are:

- Tinea capitis (ringworm of the scalp)
- Tinea corporis (ringworm of the body)
- Tinea pedis (athlete's foot)
- Tinea unguium (onychomycosis; ringworm of the nails)

Tinea cruris (ringworm of the thigh)
Tinea barbae (barber's itch)

GRIFULVIN V inhibits the growth of those genera of fungi that commonly cause ringworm infections of the hair, skin, and nails, such as:

Trichophyton rubrum
Trichophyton tonsurans
Trichophyton mentagrophytes
Trichophyton interdigitalis
Trichophyton verrucosum
Trichophyton sulphureum
Trichophyton schoenleini
Microsporum audouini
Microsporum canis
Microsporum gypseum
Epidermophyton floccosum
Trichophyton megnini
Trichophyton gallinae
Trichophyton crateriform

Note: Prior to therapy, the type of fungi responsible for the infection should be identified. The use of the drug is not justified in minor or trivial infections which will respond to topical antifungal agents alone.

It is *not* effective in:

Bacterial infections
Candidiasis (Moniliasis)
Histoplasmosis
Actinomycosis
Sporotrichosis
Chromoblastomycosis
Coccidioidomycosis
North American Blastomycosis
Cryptococcosis (Torulosis)
Tinea versicolor
Nocardiosis

Contraindications

This drug is contraindicated in patients with porphyria, hepatocellular failure, and in individuals with a history of hypersensitivity to griseofulvin.

Two cases of conjoined twins have been reported in patients taking griseofulvin during the first trimester of pregnancy. Griseofulvin should not be prescribed to pregnant patients.

Warnings

Prophylactic Usage: Safety and efficacy of prophylactic use of this drug has not been established.

Chronic feeding of griseofulvin, at levels ranging from 0.5-2.5% of the diet, resulted in the development of liver tumors in several strains of mice, particularly in males. Smaller particle sizes result in an enhanced effect. Lower oral dosage levels have not been tested. Subcutaneous administration of relatively small doses of griseofulvin once a week during the first three weeks of life has also been reported to induce hepatomata in mice. Although studies in other animal species have not yielded evidence of tumorigenicity, these studies were not of adequate design to form a basis for conclusions in this regard.

In subacute toxicity studies, orally administered griseofulvin produced hepatocellular necrosis in mice, but this has not been seen in other species. Disturbances in porphyrin metabolism have been reported in griseofulvin-treated laboratory animals. Griseofulvin has been reported to have a colchicine-like effect on mitosis and cocarcinogenicity with methylcholanthrene in cutaneous tumor induction in laboratory animals.

Reports of animal studies in the Soviet literature state that a griseofulvin preparation was found to be embryotoxic and teratogenic on oral administration to pregnant Wistar rats. Rat reproduction studies done thus far in the United States and Great Britain have been inconclusive in this regard, and additional animal reproduction studies are underway. Pups with abnormalities have been reported in the litters of a few bitches treated with griseofulvin.

Suppression of spermatogenesis has been reported to occur in rats but investigation in man failed to confirm this.

Precautions

Patients on prolonged therapy with any potent medica-

tion should be under close observation. Periodic monitoring of organ system function, including renal, hepatic and hemopoietic, should be done.

Since griseofulvin is derived from species of penicillin, the possibility of cross sensitivity with penicillin exists; however, known penicillin-sensitive patients have been treated without difficulty.

Since a photosensitivity reaction is occasionally associated with griseofulvin therapy, patients should be warned to avoid exposure to intense natural or artificial sunlight. Should a photosensitivity reaction occur, lupus erythematosus may be aggravated.

Drug Interactions: Patients on warfarin-type anticoagulant therapy may require dosage adjustment of the anticoagulant during and after griseofulvin therapy. Concomitant use of barbiturates usually depresses griseofulvin activity and may necessitate raising the dosage.

The concomitant administration of griseofulvin has been reported to reduce the efficacy of oral contraceptives and to increase the incidence of breakthrough bleeding.

Adverse Reactions

When adverse reactions occur, they are most commonly of the hypersensitivity type such as skin rashes, urticaria and rarely, angioneurotic edema, and may necessitate withdrawal of therapy and appropriate countermeasures. Paresthesias of the hands and feet have been reported rarely after extended therapy. Other side effects reported occasionally are oral thrush, nausea, vomiting, epigastric distress, diarrhea, headache, fatigue, dizziness, insomnia, mental confusion and impairment of performance of routine activities.

Proteinuria and leukopenia have been reported rarely. Administration of the drug should be discontinued if granulocytopenia occurs.

When rare, serious reactions occur with griseofulvin, they are usually associated with high dosages, long periods of therapy, or both.

Dosage and Administration

Accurate diagnosis of the infecting organism is essential. Identification should be made either by direct microscopic examination of a mounting of infected tissue in a solution of potassium hydroxide or by culture on an appropriate medium.

Medication must be continued until the infecting organism is completely eradicated as indicated by appropriate clinical or laboratory examination. Representative treatment periods are tinea capitis, 4 to 6 weeks; tinea corporis, 2 to 4 weeks; tinea pedis, 4 to 8 weeks; tinea unguium – depending on rate of growth – fingernails, at least 4 months; toenails, at least 6 months.

General measures in regard to hygiene should be observed to control sources of infection or reinfection. Concomitant use of appropriate topical agents is usually required, particularly in treatment of tinea pedis since in some forms of athlete's foot, yeasts and bacteria may be involved. Griseofulvin will not eradicate the bacterial or monilial infection.

Adults: A daily dose of 500 mg will give a satisfactory response in most patients with tinea corporis, tinea cruris, and tinea capitis.

For those fungus infections more difficult to eradicate such as tinea pedis and tinea unguium, a daily dose of 1 gram is recommended.

Children: Approximately 5 mg per pound of body weight per day is an effective dose for most children. On this basis the following dosage schedule for children is suggested:

Children weighing 30 to 50 pounds – 125 mg to 250 mg daily.

Children weighing over 50 pounds – 250 mg to 500 mg daily.

How Supplied

GRIFULVIN V 250 mg Tablets in bottles of 100 (NDC 0062-0211-60) (white, scored, imprinted "ORTHO 211").

GRIFULVIN V 500 mg Tablets in bottles of 100 (NDC 0062-0214-60) and 500 (NDC 0062-0214-70) (white,